From: Tom Curry/FPL/Corp/SB_PLC[Tom.Curry@gsk.com]
To: Stan X Hull/PharmUS/GSK@GSK[stan.x.hull@gsk.com] ; Lafmin C Morgan/PharmUS/GSK@GSK[lafmin.c.morgan@gsk.com]
CC: Ted T Geiger/PharmUS/GSK@GSK[ted.t.geiger@gsk.com] ; Duncan Learmouth/CORP/GSK@GSK[duncan.learmouth@gsk.com] ; Philip C Thomson/CORP/GSK@GSK[philip.c.thomson@gsk.com] ; Frank J Murdolo/FPL/Corp/SB_PLC@GSK[Frank.J.Murdolo@gsk.com] ; Anita E Kidgell/CORP/GSK@GSK[anita.e.kidgell@gsk.com]
BCC:
Date Sent: 7/14/2004 3:25:05 PM
Subject: JP request on Advair growth

Attachment names	Size (Kb)	Document Type
01_7_11_2004___Deutsche_B__GlaxoSmithKline_-_Breathi_wpk21522.d01.pdf	661408	Adobe PDF
02_6_24_2004___Smith_Barn__GlaxoSmithKline-_Downgrad_szd26969.d01.pdf	489874	Adobe PDF

Stan and Lafmin,

JP called regarding the recent Deutsche Bank report that focused on Advair's growth in the US.

JP believes a lot of investors on the Earnings' call will have read this report. So, for JP and David to be prepared, JP requested a summary of the major points in the DB report regarding Advair's growth opportunities and our rebuttal to those points.

I called and spoke with Ted so he will be starting on this, which is somewhat similar to answering some of the Q's Frank forwarded for our call on Friday.

Also, for your convenience, here is the Citigroup report that also recently commented on Advair and dropped their forecasted sales for Advair.

Please call if you want to discuss this.
Tom C

Global Equity Research

Company Update

Europe UK
Pharmaceuticals

Deutsche Bank

9 July 2004

GlaxoSmithKline

Reuters: **GSK.L** Bloomberg: **GSK LN** Exchange: **L** Ticker: **GSK.L**

Breathing easy over Advair?

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Slowdown in Advair places even more emphasis on pipeline delivery
An abrupt slowdown in US sales of Advair, GSK's leading drug, reflects a peaking in its asthma market share and suggests that consensus sales forecasts are significantly too high. This places yet further pressure on GSK to deliver on its pipeline if it is to shake off its discount rating. While we do see cashflow and yield attractions, we retain our neutral stance.

Advair's US prescription growth has slowed markedly
The asthma drug Seretide/Advair is GSK's No.1 drug and its key growth driver, accounting for >50% of consensus group revenue growth 2003-08E. US sales of Advair have slowed markedly during 2004 - IMS data suggests volume growth of 15% in Q2, after 22% in Q1 and >30% in H2 2003 - despite recent approvals for use in COPD and in paediatrics.

Consensus forecasts too high, although growth opportunities remain
Our analysis suggests that Advair's slowdown reflects an abrupt peaking of its asthma market share (now close to 40% of all patients treated). With growth comparisons over the rest of 2004 also strained by prior-year wholesaler stocking trends we see downside pressure on near-term sales forecasts. Looking longer term, we do see fresh growth opportunities over 2005 and 2006 from two major outcomes studies, GOAL (asthma) and TORCH (COPD). We would then expect growth to be curtailed again by the likely 2007 launch of AZN's Symbicort. Taken together, we forecast global Seretide/Advair sales of £3.5bn in 2008, c.20% below consensus expectations of >£4bn. A further risk to sentiment on Advair is a likely US patent challenge, although generics could not be launched before 2008.

Retain neutral stance; shares need pipeline newsflow
Given GSK's pedestrian near-term prospects we continue to argue for a discount rating. Our price target applies a c.10% 2005E P/E discount to the sector. Cashflow-based metrics (eg, CROCI) suggest a higher value but near-term newsflow (difficult Q2/Q3 comparisons, litigation/patent concerns, limited pipeline news) seems unlikely to unlock this value.

Forecasts and ratios

Year End Dec 31	2003	2004E	2005E	2006E
EPS (p)	**82.10**	76.70	80.50	86.90
DPS (net)	**41.00**	42.00	43.00	44.00
Div./Yield %	**3.2%**	3.9%	4.0%	4.1%
P/E x	**13.30**	14.20	13.60	12.60
EV/EBITDA x	**8.2x**	9.0x	8.8x	8.2x
Revenue	**21,441**	20,572	21,283	22,357
PBT stated (£m)	**6,719**	6,195	6,331	6,652

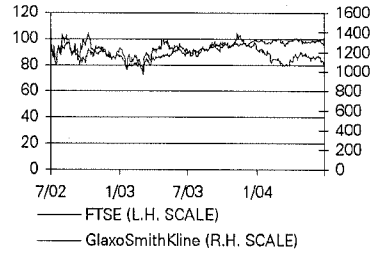
Source: Deutsche Bank estimates and company data

Primer

Hold

Price at 8 July 2004 (GBP)	**1,091.0**
Price target - 12mth (GBP)	**1200**
52-week range (GBP)	**1,390.0 - 1,060.0**

Price/price relative

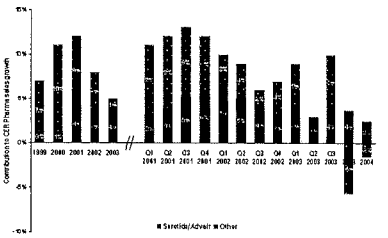


Performance (%)	1m	3m	12m
Absolute	-5.2%	-1.5%	-10.9%
FTSE	-2.7%	-2.4%	7.5%

Stock data

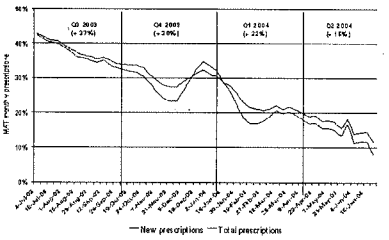
Market Cap (GBP)	**62,361**
Shares outstanding (m)	**5,716.0**
Free float	**100.0%**
Est. 5 year EPS growth	**6.0%**
FTSE	**4,381.1**
Index membership	**FTSE, STOXX**
Major shareholders: US shareholding	**22%**

Advair's contribution to Pharma growth



Source: Deutsche Bank estimates

Advair US prescription growth trends



Source: IMS and Deutsche Bank estimates

Model updated: 08 July 2004

Equity Research
Europe
UK
Pharmaceuticals

GlaxoSmithKline

Reuters: GSK.L Bloomberg: GSK LN

Hold

Price as of 08 July	GBp 1091.00
Target price	GBp 1200.00

Company website
http://www.gsk.com

Company description

GlaxoSmithKline is a research-based pharmaceutical group that develops, manufactures and markets vaccines, prescription and over-the-counter medicines, as well as health-related consumer products. GSK has leadership in four major therapeutic areas anti-infectives, central nervous system, respiratory and gastro-intestinal/metabolic and also has a growing portfolio of oncology products. GSK was formed in 2000 through the merger of Glaxo Wellcome and SmithKline Beecham and currently ranks second in market capitalisation within the global pharmaceutical industry.

Research Team

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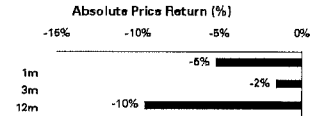
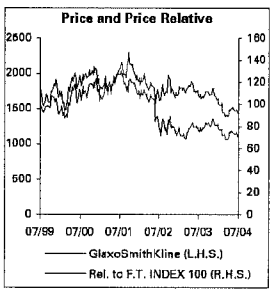
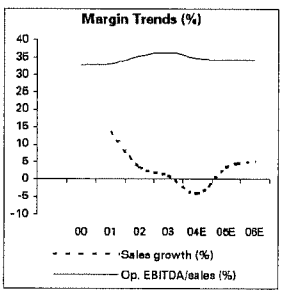


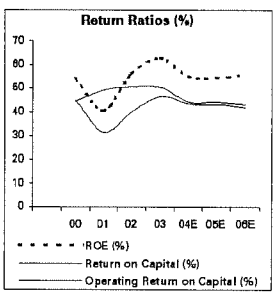
52-week Range:	GBp1060.00 - 1390.00
Market Cap (m)	GBP 62,362
	USD 115,849

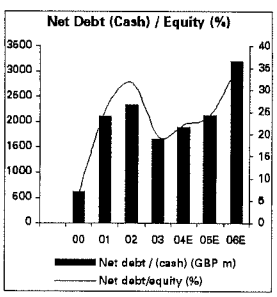
Company identifiers	
Cusip	NA
SEDOL	0925288

Year Ending 31 December	2000	2001	2002	2003	2004E	2005E	2006E
SUMMARY							
Headline EPS (GBp)	60.96	72.30	78.26	82.08	76.70	80.46	86.88
P/E ratio Headline (x)	30.6	25.8	18.3	15.0	14.2	13.6	12.6
Headline EPS growth (%)	15.7	18.6	8.3	4.9	-6.5	4.9	8.0
EPS FD (GBp)	68.49	50.33	66.22	77.24	76.68	80.46	86.88
P/E ratio FD (x)	27.3	37.0	21.6	15.9	14.2	13.6	12.6
Operating CFPS (GBp)	64.90	76.39	91.46	83.88	89.16	94.99	84.65
Free CFPS (GBp)	49.05	59.08	74.80	69.71	74.29	78.82	66.19
P/CFPS (x)	28.8	24.4	15.6	14.6	12.2	11.5	12.9
DPS (GBp)	38.00	39.00	40.00	41.00	42.00	43.00	44.00
Dividend yield (%)	2.0	2.1	2.8	3.3	3.8	3.9	4.0
BV/Share (GBp)	127.14	121.85	111.32	132.97	143.52	148.91	159.00
Price/BV (x)	14.87	14.14	10.71	9.63	7.60	7.33	6.86
Weighted average shares (m)	6,065	6,085	5,912	5,806	5,716	5,566	5,416
Average market cap (GBP m)	113,253	113,020	84,499	71,256	62,362	62,362	62,362
Enterprise Value (GBP m)	112,564	112,755	84,520	70,580	61,441	61,613	62,645
EV/Sales	6.23	5.50	3.98	3.29	2.99	2.89	2.80
EV/EBITDA	19.0	16.6	11.3	9.0	8.6	8.5	8.2
EV/EBIT	21.2	18.5	12.8	10.4	9.9	9.7	9.3
EV/Operating Capital	13.0	11.9	9.0	7.0	6.0	5.8	5.3
INCOME STATEMENT (GBP m)							
Sales revenue	18,079	20,489	21,212	21,441	20,572	21,283	22,357
Operating EBITDA	5,926	6,803	7,492	7,808	7,123	7,291	7,674
Depreciation	626	713	909	1,021	888	925	963
Amortisation	0	0	0	0	1	0	0
EBIT	5,300	6,090	6,583	6,787	6,233	6,366	6,711
Net interest income (expense)	-192	-88	-141	-161	-140	-140	-170
Associates/affiliates	65	71	75	93	101	106	111
Investment and other inc./exp.	144	96	0	0	0	0	0
Exceptionals/extraordinaries	457	-1,332	-712	-281	0	0	0
Income tax expense	1,454	1,663	1,760	1,848	1,704	1,741	1,829
Minorities/preference dividends	176	131	130	106	107	112	117
Net income	4,154	3,053	3,915	4,484	4,383	4,478	4,706
CASH FLOW (GBP m)							
Cash flow from operations	3,936	4,633	5,407	4,870	5,096	5,287	4,585
Movement in net working capital	297	67	98	697	300	310	326
Capex	-961	-1,050	-985	-823	-850	-900	-1,000
Free cash flow	2,975	3,583	4,422	4,047	4,246	4,387	3,585
Other investing activities	-42,374	-847	-209	-143	-150	-150	-150
Equity raised/(bought back)	43,259	-1,731	-2,106	-954	-1,500	-2,000	-2,000
Dividends paid	-2,028	-2,325	-2,327	-2,333	-2,393	-2,453	-2,512
Net inc/(dec) in borrowings	4,032	200	411	460	0	0	0
Other financing cash flows	-56	-34	-20	-12	-8	-8	-7
Total cash flows from financing	45,207	-3,890	-4,042	-2,839	-3,901	-4,461	-4,519
Net cash flow	5,808	-1,154	171	1,065	195	-224	-1,085
Movement in net debt/(cash)	-1,776	1,354	240	-605	-195	224	1,085
BALANCE SHEET (GBP m)							
Cash and other liquid assets	3,421	2,131	2,308	3,455	3,211	2,987	1,901
Tangible fixed assets	6,642	6,845	6,649	6,441	6,403	6,378	6,416
Goodwill	170	174	171	143	143	143	143
Other intangible assets	966	1,673	1,697	1,697	1,847	1,997	2,147
Associates/investments	2,544	3,228	3,121	3,069	3,168	3,271	3,380
Other assets	7,947	8,292	8,441	9,170	9,470	9,780	10,106
Total assets	21,590	22,343	22,327	23,975	24,241	24,556	24,092
Interest bearing debt	4,032	4,232	4,643	5,103	5,103	5,103	5,103
Other liabilities	8,603	9,859	10,296	10,407	10,580	10,758	9,917
Total liabilities	12,635	14,091	14,939	15,510	15,683	15,861	15,020
Shareholders' equity	7,711	7,390	6,581	7,720	8,204	8,289	8,611
Minorities	1,244	862	807	745	355	407	461
Total shareholders' equity	8,955	8,252	7,388	8,465	8,558	8,695	9,072
Net working capital	873	801	1,023	1,861	2,188	2,520	3,888
Net debt(cash)	611	2,101	2,335	1,648	1,892	2,116	3,202
Capital	9,566	10,353	9,723	10,113	10,451	10,811	12,274
RATIO ANALYSIS							
Sales growth (%)	nm	13.3	3.5	1.1	-4.1	3.5	5.0
Op. EBITDA/sales (%)	32.8	33.2	35.3	36.4	34.6	34.3	34.3
EBIT/sales (%)	29.3	29.7	31.0	31.7	30.3	29.9	30.0
Payout ratio (%)	62	54	51	50	55	53	51
ROE (%)	53.9	40.4	56.0	62.7	55.1	54.3	55.7
Return on Capital (%)	44.8	31.3	40.0	45.4	43.6	43.1	41.8
Operating Return on Capital (%)	44.4	49.1	50.8	50.4	44.3	44.2	43.3
Capex/sales (%)	5.3	5.1	4.6	3.9	4.1	4.2	4.5
Capex/depreciation (x)	1.5	1.5	1.1	0.9	1.0	1.0	1.0
Net debt/equity (%)	6.8	25.5	31.6	19.5	22.1	24.3	35.3
Net interest cover (x)	29.1	69.2	46.7	42.2	44.5	45.5	39.5









Source: Company data, Deutsche Bank estimates

Investment thesis

Outlook

GlaxoSmithKline is the world's No. 2 drug company with a near-7% market share. In the first year after its merger, its performance was encouraging, with 2001 sales and EPS growth of 12% and 14%, respectively, in constant currency terms. By 2003, Pharma sales growth had slipped to just 5%, although the last tranche of merger savings allowed EPS to rise by 10%. The marked sales slowdown reflected the early onset of generic competition to GSK's lead antibiotic Augmentin, in 2002, and to its lead anti-depressant Paxil, in 2003. Each followed successful patent challenges by generic companies. Given the timing of the arrival of Paxil generics (in September 2003) and the Q1 2004 launch of generics to GSK's No. 2 anti-depressant Wellbutrin (yet again, following a patent challenge), 2004 will be a tough year for GSK. Company guidance for this 'transition year' is for EPS to be at least in line – in constant exchange rate terms - with the business performance in 2003 (ie, 82.1p). The latter included a raft of non-recurring charges in Q4 (totaling £401m or 5p per share) which should ensure that this target is achieved without undue difficulty. Meanwhile, GSK continues to work hard to (as its respected CEO, J-P Garnier, puts it) "*build the best pipeline in the industry*". The first opportunity to present this pipeline in detail was at last December's R&D Day. In the event, this turned out to be a somewhat mixed affair, with news of a further sizeable uplift in the number of pipeline candidates more than counter-balanced by delays for certain projects and generally distant submission timelines for the majority of compounds. Later this year, however, Phase II data should emerge on several important pipeline candidates (respectively for depression, pain and rhinitis) and in early 2005 we expect Phase III results for the potentially exciting breast cancer drug 572016.

Valuation

We have consistently argued that GSK's shares deserve no more than P/E parity with the drugs sector on our longer-term EPS forecasts, given its unspectacular medium-term growth prospects (2003-07E EPS CAGR 3%) and the still-unproven nature of its large but early-stage R&D pipeline. Putting the shares at a 10-15% P/E discount to the sector on 2005E EPS would imply fair value in the range of 1140-1210p and our established target price is at the top end of this range, at 1200p. The shares (at 1091p) are currently around 9% below our target price. Using DB's CROCI (Cash return on Capital Invested) methodology – which can be used to determine absolute rather than relative value - suggests a value of 1350p. Taking the two methodologies together suggests that the shares are somewhat undervalued but we do not feel confident that near-term newsflow (difficult Q2 and Q3 comparisons, litigation and patent concerns, limited pipeline news) will unlock this value quickly and thus retain our 'Hold'.

Risks

We judge the key downside risks to our neutral stance to be those that apply to the majority of other large-cap pharma companies, namely patent losses and challenges and R&D setbacks. In addition, continuing US dollar volatility represents a continuing risk to EPS forecasts (although this is also true for most of GSK's European peers). The principal upside risk in our view could come from positive developments in R&D and from legal victories on key drug patents.

Table of contents

Advair's importance to GSK

Seretide/Advair accounts for 14% of GSK's Pharma sales ...

GSK's respiratory drug Advair, marketed as Seretide in Europe, combines the long-acting bronchodilator salmeterol (Serevent) with the inhaled steroid fluticasone (Flixtode/Flovent). Launched in 2000 in Europe and in April 2001 in the US, Seretide/Advair is now the company's top-selling product, accounting for 14% of Q1 2004 Pharma sales. With 2004 sales forecast at £2.45bn ($4.4bn), we estimate that it will rise two places to become the industry's No.5 selling product (Figure 1).

Figure 1: Top ten global pharmaceuticals by sales, 2004E ($m)

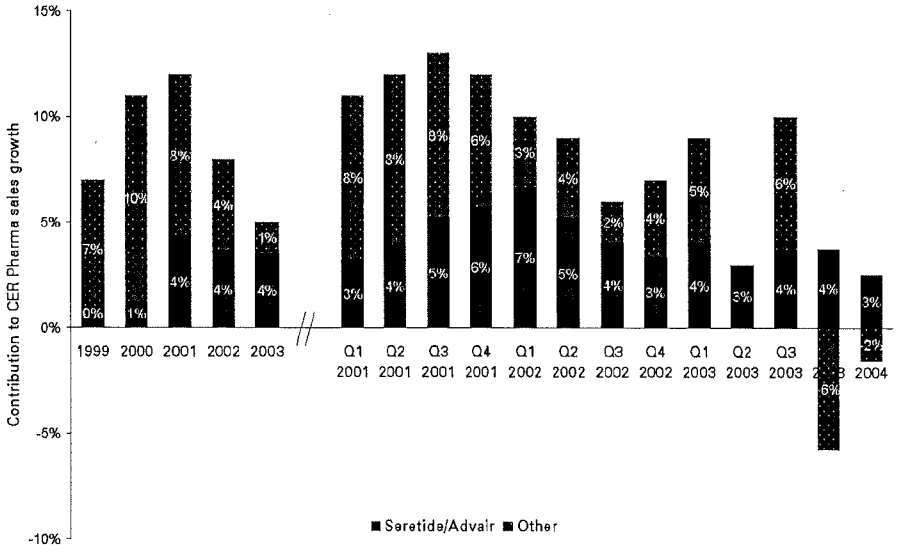
Rank	Product	Company	2004E sales ($m)
1	Lipitor	Pfizer	10,400
2	Zocor	Merck	5,000
3	Plavix	Sanofi/Bristol-Myers Squibb	4,850
4	Norvasc	Pfizer	4,700
5	Seretide/Advair	GSK	4,410
6	Zyprexa	Lilly	4,375
7	Nexium	AstraZeneca	4,231
8	Procrit/Eprex	Johnson & Johnson	3,884
9	Zoloft	Pfizer	3,210
10	Effexor	Wyeth	3,165

Source: Deutsche Bank

...and has driven half of GSK's growth in recent years

We calculate that Seretide/Advair has been responsible for half of GSK's Pharma growth over the past three years (Figure 2).

Figure 2: Contribution of Seretide/Advair to Pharma CER sales growth



Source: company data and Deutsche Bank estimates

Furthermore, consensus market forecasts (as supplied to us by GSK) suggest that Seretide/Advair will continue to be responsible for around half of GSK's group sales growth over the next five years (Figure 3).

Figure 3: Consensus sales forecasts for Seretide/Advair and GSK (£bn)

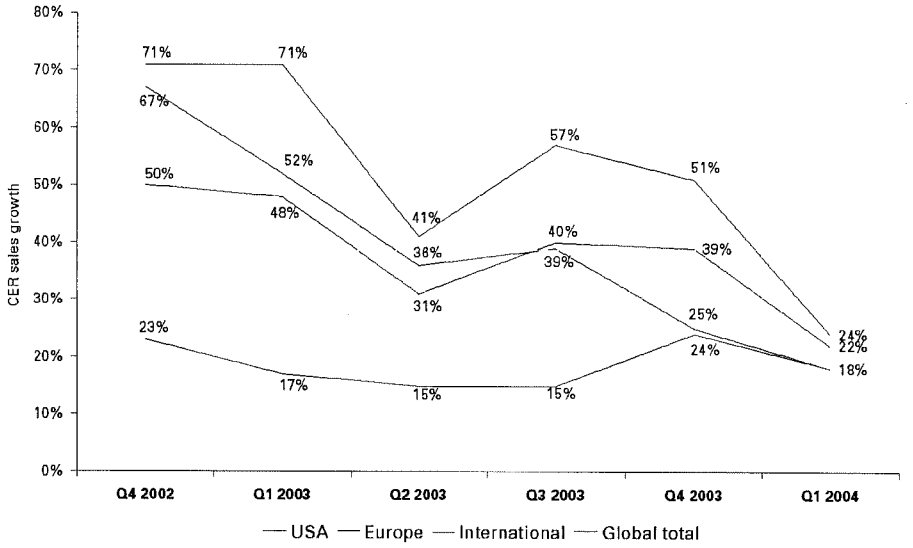
£bn	2003	2004E	2005E	2006E	2007E	2008E	Change 2003-08E
Seretide/Advair	2.21	2.63	3.14	3.60	3.90	4.40	2.19
GSK group sales	21.44	20.88	21.92	23.05	24.23	25.68	4.24
Seretide/Advair as % growth	255%	n/a	49%	41%	25%	34%	52%

Source: GlaxoSmithKline

Sales growth has slowed markedly in 2004

Seretide/Advair's growth has, however, slowed noticeably recently, slipping to 22% in Q1 2004 as compared with the 39% CER growth reported in 2003 (Figure 4).

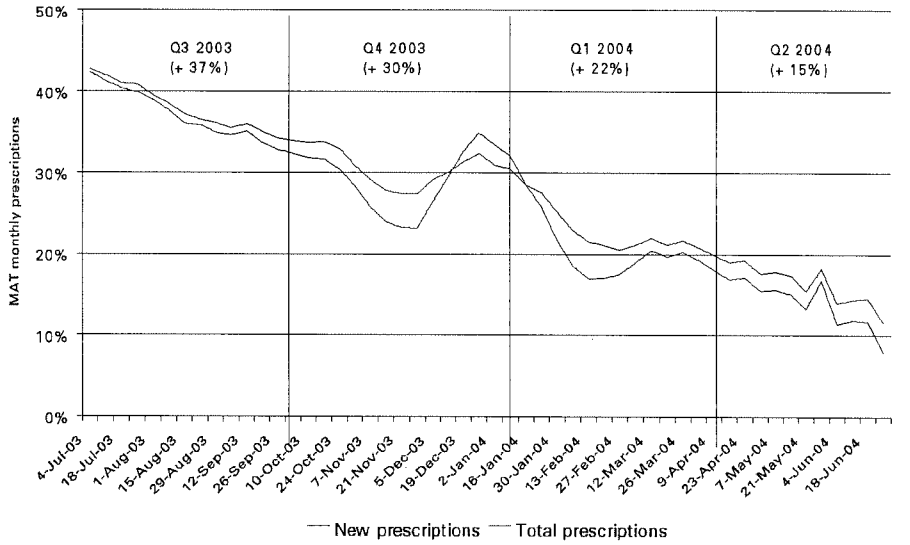
Figure 4: CER sales growth of Seretide/Advair by region since Q4 2002



Source: company data

The principal area of slowdown has been the US, where growth slowed from 54% in 2003 to 24% in Q1 2004, despite the long-awaited approval of the drug in November 2003 for use in COPD (chronic obstructive pulmonary disease). We suspect US wholesaler stocking trends distorted the apparent Q3 and Q4 2003 growth rates, as reported growth numbers of 57% and 51% respectively were substantially in excess of the 37% and 30% growth figures indicated by IMS prescription data (Figure 5). Nevertheless IMS data also shows a sustained downtrend in Advair's prescription growth over the past few quarters, with Q1 2004 growth slipping to 22% and Q2 showing a further deceleration to around 15% (with monthly MAT growth falling to 12% by end-June). Of note, the continued slowdown in Q2 has been evident despite GSK's receipt in April of approval for the use of Advair in paediatric asthma (ie, ages 4-11). Thus the two key indication extensions for Advair received over the past eight months appear to have done little or nothing to halt the slide in the drug's growth.

Figure 5: Advair US prescription growth is faltering (monthly MAT)

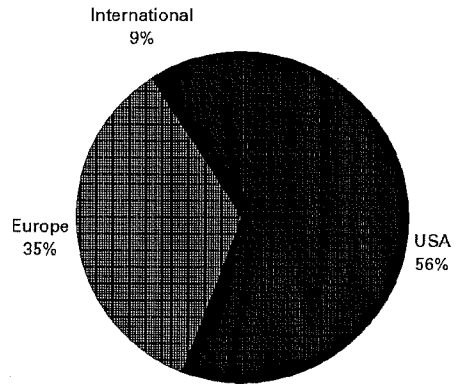


Source: Deutsche Bank

The US accounts for >50% of Seretide/Advair's sales

Given that the US accounts for over half of Seretide/Advair sales (Figure 6) this marked slippage in growth is of considerable concern and *prima facie* suggests that the consensus forecasts shown in Figure 3 – which imply a CAGR in global sales of 18% over three years and 15% over five – could well prove overly optimistic. The purpose of this report is therefore to examine Advair's prospects in the crucial US market and to assess whether consensus expectations are indeed too rosy.

Figure 6: Geographic split of Seretide/Advair sales, 2003



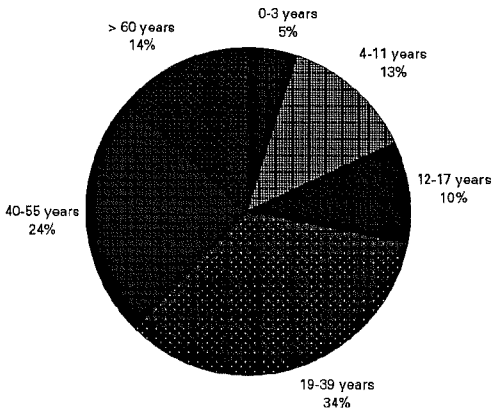
Source: company data

Asthma penetration peaking

Background

Around 20 million Americans, or 7% of the population, suffer from asthma (source: NHIS Study 2001). Of these, close to two-thirds are aged under 40 (Figure 7) and just over a quarter are children and adolescents (ie, aged under 18). The incidence of asthma is growing at an estimated 4% pa in the US.

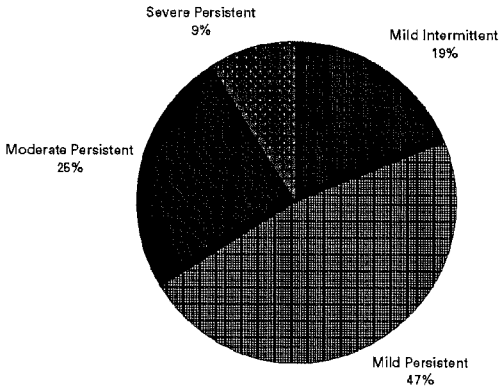
Figure 7: Distribution of asthma patients (n= 20 million) in US by age group



Source: NHIS, GlaxoSmithKline, Deutsche Bank estimates

Asthma is classified by short-term symptom observation into mild intermittent, mild persistent, moderate persistent and severe persistent. Approximately two-thirds of patients fall into the two mild categories (Figure 8).

Figure 8: Distribution of US asthma patients by disease severity



Source: Surveillance Data Inc. as cited by GlaxoSmithKline

Treatment of asthma tends to follow a step-wise approach, based on recognised disease management guidelines (Figure 9). Patients with mild intermittent asthma primarily use short-acting beta2-agonist bronchodilators (mainly salbutamol/albuterol) on as 'as needed' basis. Increasing symptom frequency that results in daily use of such drugs indicates that the patient has mild persistent asthma at which point a low-dose inhaled steroid or an alternative anti-inflammatory agent tends to be added in. Moderate and severe disease require the stepping up of steroid dosage and the addition of a long-acting beta2-agonist, such as GSK's Serevent or of course via Advair. Note that strict adherence to the US guidelines would imply that Advair usage should be confined to patients with moderate and severe persistent disease.

Figure 9: US asthma management guidelines (NHLBI)

			Asthma management guidelines	
Asthma classification	**Clinical features (before treatment)**	**Lung function**	**Long-term control (daily medications)**	**Quick relief (intermittent)**
Mild Intermittent	Symptoms ≤2 days per week, asymptomatic and normal PEF between exacerbations, brief exacerbations with varying intensity, nighttime symptoms ≤2 nights per month	FEV1/PEF ≥80% predicted PEF variability <20%	No daily medication needed	Inhaled short-acting B2-agonist as needed Intensity of treatment depends on severity of exacerbations Daily use of short-acting B2-agonist, or increasing usage, indicates need to start or increase long-term control therapy
Mild Persistent	Symptoms >2 times per week but <1 time per day, exacerbations may affect activity, nighttime symptoms >2 nights per month	FEV1/PEF ≥80% predicted PEF variability 20-30%	Low dose inhaled corticosteroid Alternatives: cromolyn, leukotriene modifier, nedocromil, OR sust-rel theophylline	As for Mild Intermittent
Moderate Persistent	Daily symptoms, daily use of inhaled short-acting B2-agonist, exacerbations ≥2 times per week that affect activity and may lsst days, nighttime symptoms >1 night per week	FEV1/PEF 60-80% predicted PEF variability >30%	Inhaled corticosteroid (low-to-medium dose) AND long-acting inhaled B2-agonist Alternatives: increase inhaled corticosteroid within medium-dose range OR inhaled corticosteroid (low-to-medium dose) and either leukotriene modifier or theophylline If needed (esp in patients with recurring severe exacerbations): Increase inhaled corticosteroid within medium dose range, AND add long-acting inhaled B2-agonist Alternatives: increase inhaled corticosteroid in medium-dose range, AND add either leukotriene modifier or theophylline	As for Mild Intermittent
Severe Persistent	Continual daytime symptoms, limited physical activity, frequent exacerbations and frequent nighttime symptoms	FEV1/PEF ≤60% predicted PEF variability >30%	Inhaled corticoteroid (high dose) AND long-acting inhaled B2-agonist AND if needed: corticosteroid tabs or syrup long-term; repeatedly attempt to reduce systemic dose and maintain control with high-dose inhaled corticosteroid	As for Mild Intermittent

Source: US Monthly Prescribing Reference

Advair's penetration in asthma

Advair has been very successful in penetrating the US asthma market. Although IMS sales data does not clearly separate out asthma from COPD prescriptions (due to the overlap in treatment), Figure 10 shows that Advair is the dominant product in the US respiratory market, accounting for close to 30% of overall sales. Only Merck's leukotriene antagonist Singulair also breaches the $1bn sales mark.

Figure 10: US asthma and COPD market, 2003 ($m)

Year to December 2003	Retail	Non-retail	Total	% total
Inhaled steroids (plain/combo)	**3,309.5**	**455.2**	**3,764.7**	**46.6%**
Advair	2,073.2	241.1	2,314.3	28.6%
Flovent	529.7	113.5	643.2	8.0%
Pulmicort	519.0	54.3	573.3	7.1%
Azmacort	114.8	27.0	141.8	1.8%
Aerobid	50.0	9.1	59.1	0.7%
Others	22.8	10.2	33.0	0.4%
Beta2-agonists	**1,042.0**	**281.9**	**1,323.9**	**16.4%**
Serevent	154.8	61.4	216.2	2.7%
Foredil	51.0	5.6	56.6	0.7%
Brethine	5.6	41.7	47.3	0.6%
Branded and generic salbutamol/albuterol	830.6	173.2	1,003.8	12.4%
Leukotriene antagonists	**1,724.9**	**123.0**	**1,847.9**	**22.9%**
Singulair	1,632.8	116.0	1,748.8	21.6%
Accolate	92.1	7.0	99.1	1.2%
Anti-cholinergics	**765.3**	**230.0**	**995.3**	**12.3%**
Combivent	430.2	106.4	536.6	6.6%
Atrovent	176.4	49.3	225.7	2.8%
Duoneb	104.4	44.5	148.9	1.8%
Generic ipratropium	54.3	29.8	84.1	1.0%
Xanthines	**83.2**	**26.6**	**109.8**	**1.4%**
Uniphyl	30.0	1.7	31.7	0.4%
Theo-24	16.1	3.5	19.6	0.2%
Generic theophylline	37.1	21.4	58.5	0.7%
Other ant-inflammatory	**40.2**	**4.5**	**44.7**	**0.6%**
Intal	22.9	2.7	25.6	0.3%
Generic cromolyn, Tilade, others	12.0	1.1	13.1	0.2%
Xolair	5.3	0.7	6.0	0.1%
Total	**6,965.1**	**1,121.2**	**8,086.3**	**100.0%**

Source: IMS Health Bank

Allowing for patients receiving multiple therapies, we estimate that Advair is used in just under 40% of asthma patients in the US. Its penetration of the various disease categories ranges from a low of around 5% in mild intermittent asthma to a high of 55% in moderate and severe persistent asthma (Figure 11). In the category that represents by far the largest proportion of diagnosed patients, namely mild persistent asthma, Advair's market share is around 40%. This is despite the drug not being recommended in the guidelines for this level of disease severity.

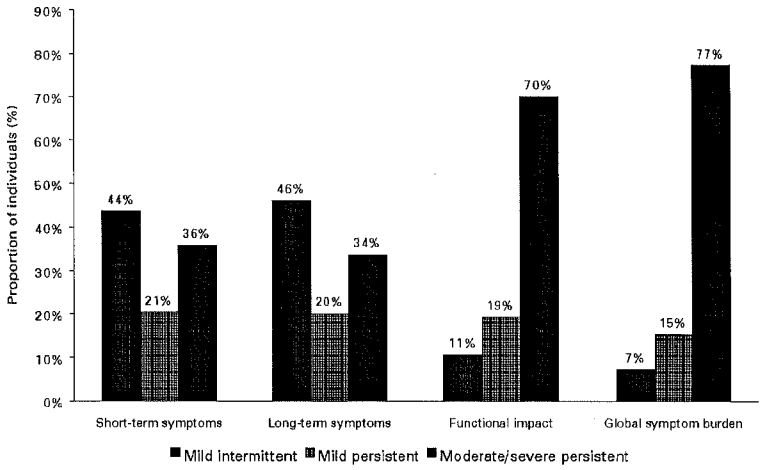
Figure 11: Asthma severity and Advair market shares

Asthma classification	% of total patients treated	Estimated Advair share
Mild Intermittent	19%	5%
Mild Persistent	47%	40%
Moderate Persistent	25%	55%
Severe Persistent	9%	55%
Total	100%	38%

Source: GlaxoSmithKline and Deutsche Bank estimates

There is a growing debate, however, about the appropriateness of disease categorisation when measured purely by short-term symptoms. A landmark 2002 study by Fuhlbrigge et al ('The burden of Asthma in the United States', *Am J Respir Crit Care Med* Vol. 166 pp 1044-1049) strongly suggests that a large number of patients diagnosed as 'mild' should in fact be classified as 'moderate-to-severe' based on a more rigorous assessment of the functional impact of their asthma on their lives. Specifically, in this 1,800 patient study, 67% of patients were classified as mild based on reported daily and nocturnal symptoms over the previous four weeks. However the proportion fell to 30% when the clinical assessment also took into account the functional impact (physical, social, and nocturnal) on patients' lives and just 22% if long-term symptoms (eg, frequency of exacerbations over a 12-month period) were also considered (Figure 12). This clearly suggests that patients diagnosed as mild should be more broadly assessed for their disease severity and that more aggressive (steroid-containing) therapy may often be warranted.

Figure 12: Underestimation of asthma severity in the US



Source: GlaxoSmithKline presentation of data from American Journal of Respiratory Critical Care Medicine 2002; 166: 1044-49

Advair's growth has slowed abruptly in asthma

Verispan data cited by GSK suggests that the percentage of Advair's US sales accounted for by COPD jumped from 16-17% in mid-2003 to just over 20% in Q1 2004. Given the slowdown in Advair's overall sales growth, we calculate that this implies that sales in the asthma setting have slowed dramatically in 2004, from around 50% growth in 2003 to 19% in Q1 2004. Furthermore, the continued slowdown in Advair's prescription growth in Q2 implies that sales growth in asthma may have slowed to just 10% year-on-year (Figure 13). Repeating the same calculations using IMS data, which suggests that the proportion of sales from COPD has in fact leaped from 20% in Q4 2004 to 28% in Q1 2004 would imply even slower growth in the asthma setting, of around 14% in Q1 2004 and 6% in Q2.

Figure 13: Advair has slowed markedly in asthma in 2004

	2002	2003	Q1 2004	Q2 2004E
Advair sales growth (GSK)	nm	54%	24%	17%
% sales in COPD (Verispan)	16%	17%	21%	22%
% sales in asthma (Verispan)	84%	83%	80%	78%
Implied growth in asthma sales	nm	52%	19%	10%
Implied growth in COPD sales	nm	64%	50%	51%

Source: Deutsche Bank estimates and Verispan data (as supplied by GSK)

In assessing this marked slowdown in the asthma setting, we understand that GSK believes it may have devoted too high a proportion of its marketing resources behind the new (and smaller) COPD indication. This could well lead to a re-deployment of resources back to the asthma indication in the relatively near term. Certainly, from our discussions with the company, we believe that GSK foresees the biggest single opportunity for Advair to be expanding sales in the mild asthma setting rather than COPD. Here GSK hopes to exploit two factors: first, a growing body of clinical data in mild asthma (for example, it has trial results that show that continued treatment with Advair in mild patients provides better asthma control compared to abbreviated control on Advair followed by a switch to Flovent, Serevent or Singulair); and second, the aforementioned debate over mis-diagnosis of patients as 'mild' which could lead to more aggressive therapy.

We are less optimistic, however, that a shift in marketing resources will lead to a major rebound in growth in asthma, at least over the remainder of 2004. We find it difficult to believe that the steroid-based asthma market is in fact very promotionally-sensitive given the limited competition that GSK faces in this category (Figure 10 showed that Advair and Flovent constitute c.80% of steroid sales in the US respiratory market). Furthermore, we believe an equally – if not more - valid explanation for Advair's abrupt slowdown in the asthma setting is simply that the drug has been so successful in such a short space of time:

- In the severe persistent setting, Advair's penetration has in our view neared its peak. From our discussions with GSK, we believe the company feels it will be difficult to move share beyond 60%, as compared with c.55% currently.
- In the moderate persistent setting, Advair's penetration is also high, at around 55%, although we see scope for further share expansion with new clinical data (see discussion of GOAL study below). We believe share could ultimately reach around 60% (based on steroid penetration of 80% and Advair increasing its share within the steroid category to around 75%).
- In the mild persistent setting, Advair's penetration of around 40% must also be considered fairly high, given that usage of the drug in this patient group would not follow from strict adherence to the treatment guidelines. Indeed, GSK acknowledged in our discussions that it will take time to build further share here. We also note that the low-dose formulation of Advair (100/50), typically used in milder patients, is the slowest growing according to IMS data.
- We see little or no opportunity to expand use in the mild intermittent setting in which treatment with Advair is largely inappropriate and not recommended.

A further challenge to the US growth of Advair over the remainder of 2004 follows from the tough wholesaler-inflated comparisons in H2 2003. As noted earlier, GSK reported US sales growth of over 50% in each of Q3 and Q4 2003 whereas IMS indicated volume growth respectively of around 37% in Q3 and 30% in Q4. Unless similar wholesaler stocking trends are seen in H2 2004, this will clearly impact on Advair's quarterly reported growth rates. We are, however, much more optimistic that GSK can at least stabilise the prescription growth trend for Advair in 2005, based on the opportunity afforded by the GOAL study.

GOAL could provide the next impetus to growth

In our view, GSK has a major marketing opportunity in 2005 when it expects to unveil the results of a major 3,500-patient outcome study, known as GOAL (Gaining Optimal Asthma ControL). This trial assesses the use of Advair across differing

severities of asthma and asks the question "is total control or clinical remission of asthma achievable". GSK has used a very exacting definition for total control that includes all the following criteria (which must be maintained for at least seven out of eight consecutive weeks when assessed over an 8-week closing period):

- Normal lung function (morning PEF ≥80% predicted)
- No daily symptoms
- No exacerbations
- No night-time awakenings due to asthma
- No rescue medication (salbutamol)
- No emergency hospital visits
- No treatment-related adverse events forcing a change in therapy.

The complex study design includes three groups of just over 1,000 patients of which one was initially steroid treatment-naïve, one had previously been treated with a low dose of inhaled steroid, and one had previously been treated with a moderate dose of inhaled steroid. In effect these groups reflect differing levels of asthma severity as indicated by the level of baseline steroid therapy. Patients in each were then randomised to receive either Advair or Flovent and treatment was stepped up every 12 weeks until patients reached total control. Patients then remained on this dose for the rest of the one-year double-blind period. An analysis was conducted in the final eight weeks of the study on all patients who had previously achieved total control to identify if total control had been maintained.

While the full results from GOAL are expected early next year, some preliminary findings have already been presented at medical meetings (EAACI, AAAAI) in 2004 (Figure 14). These showed that: (1) in all groups Advair allowed the majority of patients to be symptom-free and not in need of rescue medication for more than half the time (note that these end-points are not as exacting as for the full trial); (2) Advair numerically outperformed Flovent on each of these two efficacy parameters (although p significance values were not divulged); (3) the more intense the level of prior steroid-based therapy (ie, the more severe the disease), the worse the level of disease control; and (4) adverse event rates between the two drugs were similar.

Figure 14: Early data from GOAL study

	Advair	Flovent	% difference
Steroid-naive			
No symptoms for > half of the time	72%	66%	6%
No need for rescue medication for > half of the time	86%	77%	9%
Overall rate of adverse events	56%	55%	1%
Rate of serious adverse events	2%	4%	-2%
Low-dose prior steroid therapy			
No symptoms for > half of the time	66%	51%	15%
No need for rescue medication for > half of the time	81%	66%	15%
Overall rate of adverse events	60%	57%	3%
Rate of serious adverse events	3%	2%	1%
Moderate dose prior steroid therapy			
No symptoms for > half of the time	54%	40%	14%
No need for rescue medication for > half of the time	71%	57%	14%
Overall rate of adverse events	69%	67%	2%
Rate of serious adverse events	6%	4%	2%

Source: EAACI 2004, AAAAI 2004

The trial has been completed and the results submitted for publication. Assuming the full results are positive – which seems likely given the recent remarks of the international coordinator, Dr Eric Bateman, that *"we can say for sure that there will be a significant proportion of patients who can enjoy an asthma free status"* (source: Medical Post, 17 February 2004) – then we would expect this to result in increased share for Advair in the moderate intermittent category. Depending on the precise details of the data, this could also spur growth in share in the larger mild intermittent setting (although this might require a guideline change). Growth in the asthma setting overall would then be likely to continue until at least 2007 when we expect AstraZeneca's competitor combination drug Symbicort to be launched in the US (we do not believe Aventis/Altana's steroid Alvesco – which was filed in December 2003 and could be launched in late-2005 or 2006 - poses any significant threat as it is a plain steroid).

AstraZeneca's Symbicort is a longer-term threat

Symbicort is essentially a look-alike of Seretide/Advair, combining the long-acting bronchodilator Oxis (formoterol) with the steroid Pulmicort (budesonide) in the breath-actuated Turbuhaler device. The drug has been launched in over 60 countries, including all the major European territories (where its first launches began in 2001), but it is not yet available in the US (see below).

The principal therapeutic difference between Advair and Symbicort is that the bronchodilator component of Symbicort has a fast onset of action (<15 minutes versus 30-48 minutes with the Serevent component of Advair). This has allowed AstraZeneca to devise a more tailor-made approach to therapy which it terms 'adjustable maintenance dosing'. Essentially, this does away with the need for a separate fast-acting bronchodilator and allows the patient to vary his/her medication with the severity of symptoms (ie, it allows the patient to switch between once- and twice-daily inhalation of Symbicort, depending on whether the need is for base-line therapy or for treating exacerbations). AstraZeneca has branded this new approach 'Symbicort Single Inhaler Therapy' (SiT) and submitted this for approval in the EU in November 2003. If approved – which is far from guaranteed as the regulators may feel it places too much emphasis on the patient to monitor their own disease - we would expect this patient-friendly (and cost-effective) concept to help Symbicort to expand its current c.25% share of the European combination therapy market. In support of the SiT concept, AstraZeneca has cited, amongst others, the SUND study in 658 moderate-to-severe asthmatic patients (Aalbers; *Curr Med Res Opin* 2004; 20(2)). This showed that adjustable maintenance dosing with Symbicort resulted in a 40% lower rate of exacerbations and 27% less use of rescue medication compared with fixed dosing with Seretide/Advair. GSK has unsurprisingly taken issue with this study as it believes that the trial design was flawed (notably it did not allow patients with worsening control to adjust their Seretide/Advair dosage upwards, which clearly does not reflect a 'real world' situation).

Development of Symbicort in the US has been very protracted and the filing date has slipped several times. We believe this reflects issues surrounding the inhaler device. While the Turbuhaler is approved in the US for delivering Pulmicort, problems with its dose-repeatability held up the FDA review for several years during the 1990s. AstraZeneca has switched to developing Symbicort in the US in a pressurised metered-dose inhaler (pMDI) and it currently targets an FDA submission for use in asthma in 2005 (and in COPD beyond 2006). We understand that the pMDI device chosen by AstraZeneca is patented and novel and consequently – based on the FDA's relatively tardy track record in this area - we conservatively

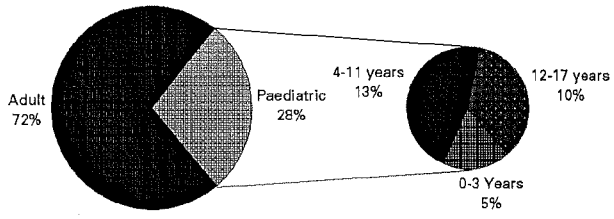
assume that the regulatory review of Symbicort will take around two years. Our best estimate is that AstraZeneca will launch Symbicort in the US during 2007.

Clearly Advair's likely six-year marketing head-start and its more extensive clinical database will mean that Symbicort is unlikely to capture a very large market share quickly. Nonetheless the newer drug's faster onset of action and the associated adjustable dosing concept are likely to prove genuinely attractive attributes to many patients and physicians and hence – in our modelling - we assume that Symbicort will capture close to a 10% market share of combination therapy in 2008.

Paediatric opportunity?

Children and adolescents represent around a quarter of diagnosed asthma sufferers (Figure 15). In absolute terms this equates to around a 6 million patient opportunity. Advair was already commercially available – as part of its original FDA approval in 2001 – for use in the 12 and over age group prior to its April 2004 approval for use in 4-11 year olds. The latter group accounts for around 13% of asthma sufferers. The fact that this latest approval appears to have had little or no impact to date on Advair's sales trajectory is likely to be explained, in our view, by a permutation of one or more of the following factors: a pre-existing significant level of 'off-label' use; the particular dynamics in this young patient group, in which steroid-related safety fears loom larger (see below); and/or the fact that GSK has been slow to market this indication, having only introduced detailing aids in June, two months after approval.

Figure 15: The US asthma market – breaking out the paediatric population



Source: GlaxoSmithKline

In terms of the dynamics within this segment of the market, Verispan estimates Advair's market share among paediatricians to be around 15%, a figure that has barely changed since mid-2002. Strikingly, this represents approximately half of its share (of c.30%) among all other key prescribing audiences (eg, primary care physicians and pulmonary and allergy specialists). The major difference in Advair's penetration is explained by the dominance in the paediatric segment of Merck's leukotriene antagonist Singulair, which enjoys a c.40% market share. As a simple once-daily tablet, Singulair offers a major convenience and compliance advantage for younger patients compared with inhaler-based therapy as well as an absence of steroid 'taint' (ie, fears over growth retardation etc). The fact that Singulair is only moderately efficacious and that it has been shown in clinical studies in adults to be

inferior to Advair (for example, 'First-line maintenance therapy in asthma: fluticasone propionate/salmeterol combination vs montelukast'. *Am J Respir Crit Care Med* 2001; 164(5):759-763) appears to have made little difference to the success of this drug. Merck reported US sales of Singulair of $1.4bn in 2003 (vs. Advair's $2.0bn) and Q1 2004 sales grew by 32% in prescription terms (aided by approval in 2003 for use in allergic rhinitis). Without head-to-head clinical data showing Advair's superiority in the children (we are not aware of any such studies being planned), we find it difficult to see what could dislodge Singulair's entrenched position and thus view the paediatric opportunity for Advair as relatively limited. Indeed, we see this as a smaller growth opportunity than both mild adult asthma and COPD.

Modelling Advair in asthma

In modelling Advair's sales in asthma (Figure 16) we make the following key assumptions:

- Growth in US asthma patient numbers is a steady 4% pa and the proportion treated with an inhaled steroid rises from 67% in 2003 to 75% by 2008, driven mainly by increasing treatment of mild adult patients.
- Advair's apparent share of inhaled steroid therapy dips slightly in 2004, given that wholesaler stocking trends appear to have over-stated 2003 sales, but rises to 62% in 2006 from 59% in 2004. Key here is the unveiling of the GOAL data in 2005. This equates to Advair's share of total treated patients in asthma rising from 37% in 2004 to 40% in 2006. GOAL could possibly also increase the average duration of therapy although we have not reflected this in our model.
- This suggests that Advair sales in asthma will grow by 10% in 2004, picking up to 15% in 2005 and 12% in 2006.
- We assume the launch of Symbicort in 2007 sees some market share loss for Advair, leading to a flattening of sales in 2007 and 2008. Over this period we see Advair's sales in asthma holding level at around $2.5bn pa.

Figure 16: Modelling Advair in the US asthma market ($m) – excludes COPD use

Sales $m	2003	2004E	2005E	2006E	2007E	2008E	CAGR
Total asthma patients (m)	20.00	20.80	21.63	22.50	23.40	24.33	4%
% treated	67%	69%	70%	72%	73%	75%	
Treated asthma patients (m)	13.48	14.33	15.23	16.18	17.17	18.23	6%
% taking steroid	63%	63%	64%	65%	65%	65%	
Steroid-treated patients (m)	8.49	9.03	9.75	10.51	11.16	11.85	7%
% Advair share of steroid-treated	60%*	59%	61%	62%	60%	55%	
Advair overall patient penetration %	38%*	37%	39%	40%	39%	36%	
% Symbicort share of steroid-treated	-	-	-	-	2%	7%	
Advair treated patients	5.10	5.33	5.95	6.52	6.64	6.52	5%
Average length of therapy (months)	3.0	3.0	3.0	3.0	3.0	3.0	0%
Total Advair scrips (m)	15.52	16.23	18.11	19.86	20.23	19.85	5%
Monthly AWP pre-discount ($)	128	134	138	141	144	146	3%
Average realised price ($)	108	114	117	120	122	124	3%
Advair revenues in asthma	1,683	1,847	2,123	2,375	2,468	2,470	8%
Yoy change	n/a	10%	15%	12%	4%	0%	
Note: Symbicort revenues in asthma					103	319	

*Note: * wholesale stocking trends inflated H2 2003 sales and we have chosen to reflect this in our model through Advair's shares of patients treated*
Source: Deutsche Bank

We discuss Advair's prospects in the US COPD market next.

Advair forecasts & conclusions

Aggregating our US asthma and COPD forecasts

Figure 25 aggregates our updated models for Advair in asthma and COPD. In summary we expect Advair's US sales to grow in the teens (in US$ terms) until 2006. Thereafter we assume that the arrival of AstraZeneca's Symbicort causes growth to flatten off. Our revised forecasts are very close (within $70m in all years) to those we have previously assumed in our GSK model. Importantly, we have not assumed a successful patent challenge and generic launch in this time-scale.

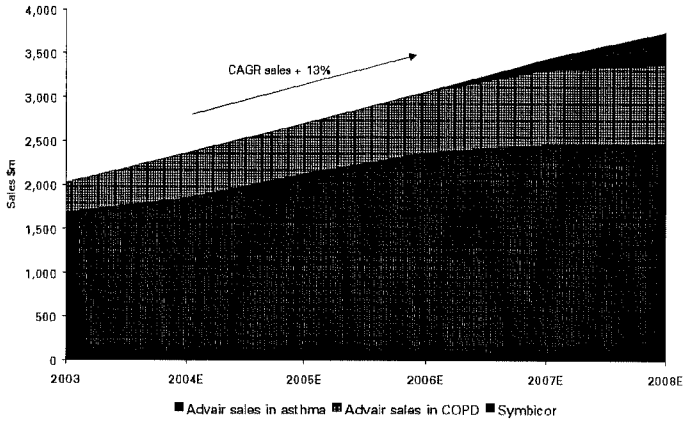
Figure 25: Summary Advair (and Symbicort) US forecasts ($m)

Sales $m	2003	2004E	2005E	2006E	2007E	2008E	CAGR
Advair sales in asthma	1,683	1,847	2,123	2,375	2,468	2,470	8%
Advair sales in COPD	342	516	579	685	846	900	21%
Total Advair sales	**2,025**	**2,363**	**2,703**	**3,060**	**3,314**	**3,370**	**11%**
yoy	54%	17%	14%	13%	8%	2%	
US$:£ rate	1.64	1.80	1.80	1.80	1.80	1.80	
Total Advair sales in £m	**1,235**	**1,313**	**1,502**	**1,700**	**1,841**	**1,872**	**9%**
Yoy		6%	14%	13%	8%	2%	
% of sales in asthma	83%	78%	79%	78%	74%	73%	
% of sales in COPD	17%	22%	21%	22%	26%	27%	
Note: Symbicort total revenues					120	372	
Symbicort share of combination revenues					3%	10%	

Source: Deutsche Bank estimates and company data

Figure 26 shows our forecasts for the US combination bronchodilator/steroid category and indicates that we expect a CAGR sales of 13% to 2008, a rate of growth that would be deemed very healthy in many other therapy areas.

Figure 26: The US combination bronchodilator/steroid market



Source: Deutsche Bank estimates and company data

Consensus global sales forecasts are too high in our view

Adding in our non-US forecasts (Figure 27), we project an 11% rise in global Seretide/Advair sales in 2004 in sterling terms, with sales ultimately reaching £3.5bn by 2008. This leaves our forecasts significantly below consensus in all future years

and >10% below consensus from 2005 on. In short, to answer our original question, we do believe market expectations for Seretide/Advair are too rosy and almost certainly based on overly optimistic US sales growth assumptions.

Figure 27: Seretide/Advair global forecasts: DB vs. consensus (£bn)

Year to December (£bn)	2003	2004E	2005E	2006E	2007E	2008E
US sales	1.24	1.31	1.50	1.70	1.84	1.87
Non-US sales	0.98	1.14	1.28	1.41	1.52	1.62
DB Advair sales	**2.21**	**2.45**	**2.78**	**3.11**	**3.37**	**3.49**
Consensus Advair (source: GSK)	**2.21**	**2.63**	**3.14**	**3.60**	**3.90**	**4.40**
Difference %	n/a	-7%	-11%	-14%	-14%	-20%

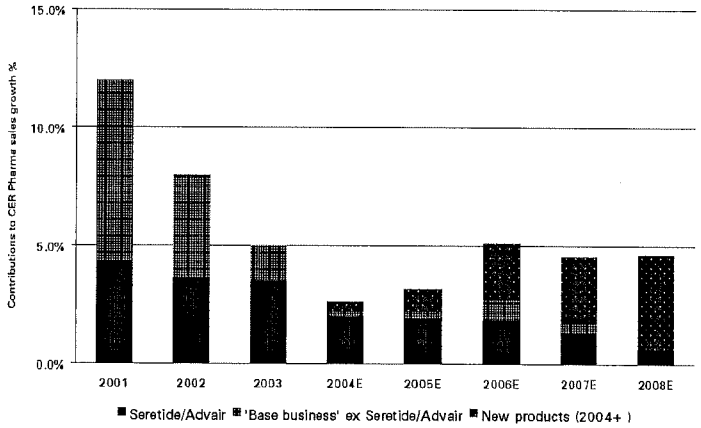
Source: Deutsche Bank estimates and company data

Concluding remarks

In conclusion, we would summarise our findings as follows:

- While we believe it would wrong to be overly bearish about recent US prescription trends for Advair - given the fresh growth opportunities afforded by the GOAL and TORCH studies in 2005 and 2006 respectively – we nevertheless believe that consensus forecasts for Seretide/Advair are significantly too high.
- In H2 2004, reported US growth could be pressurised by a short-term peaking of Advair's market share in asthma and by prior-year wholesaler stocking trends.
- Beyond 2004, we do expect Advair to sustain growth in double digits until such time as Symbicort is launched in the US, which we currently project in 2007.
- In the mean time, a challenge to Advair's US combination patent by a US partner of Cipla seems likely in our view, which could adversely impact GSK's share price. However, we cannot call the likely outcome of such a challenge and we note that generics could not be launched before February 2008. The impact of a successful challenge would hence be distant and difficult to quantify.
- All of the above will serve to increase investor focus on GSK's follow-on, once-daily 'Beyond Advair' combination, which is expected to be filed in H2 2008.
- More generally, our below-consensus forecasts for the drug imply that GSK cannot rely so heavily upon Advair to drive significant growth in future years (Figure 28), thereby placing further pressure on the R&D pipeline to deliver.

Figure 28: Advair's contribution to GSK's CER Pharma sales growth



Source: Deutsche Bank estimates and company data

citigroup

Smith Barney

See page 26 for Analyst Certification and Important Disclosures

HOLD (2)
Low Risk (L)

EQUITY RESEARCH: UNITED KINGDOM

Pharmaceuticals

Price:	**£11.61**
Target:	**£12.35**
Mkt Cap:	**£68,638.3m**

24 June 2004

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GlaxoSmithKline

Downgrade to Hold

- ***Advair*** **(asthma and COPD) and EPS forecasts cut from above to below consensus**
- ***Paxil*** **(depression) litigation likely to expand**
- **Some early pipeline news in 2H04**
- **2005E P/E discount to the sector of 20%, premium of 20% to the UK market; 2005E EPS growth of 8% versus 11% for the sector**
- **We revise our target price to 1,235p from 1,400p, based on a 15% 2005E P/E discount to the sector**
- **We downgrade to Hold/Low Risk (2L) from Buy/Low Risk (1L)**

Rating: Changed | Target Price: Changed | Estimates Changed | London (UK)

GSK.L **Price: £11.61**

Year to Dec	Sales (£m)	Net Income (£m)	EPS (p)	EPS (Old) (p)	P/E	P/E Relative	FV/ EBITDA	Net DPS (p)	Div Yield (%)
2002A	21,209	4,624	78.20	78.30	14.8	0.9	9.5	40.00	3.4
2003A	21,441	4,765	82.10	82.10	14.1	1.0	9.2	41.00	3.5
2004E	20,987	4,287	74.50	75.00	15.6	1.4	9.9	41.00	3.5
2005E	22,348	4,576	80.30	83.60	14.5	1.4	9.3	42.00	3.6
2006E	23,887	4,931	87.40	93.50	13.3	1.4	8.7	43.60	3.8

52W Price Range: £13.90 to 10.00

				Price Performance (%)	Ytd	1m	3m	12m
Expected Share Price Return	6.4%	Shares Outstanding	5,912.0m	Absolute	-7.10	0.70	10.60	-3.30
Expected Dividend Yield	3.5%	Market Cap.	£68,638.3m	Relative to Local	-7.87	-1.08	6.16	-16.34
Expected Total Return	9.9%	ROE (Curr Yr)	67%	Relative to DJ STOXX	-13.8	-1.46	5.27	-16.35

Sources: Company reports and Smith Barney estimates

Citigroup Global Markets

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Following our significant reductions in Advair sales forecasts and, consequently, EPS forecasts, we downgrade our recommendation to Hold/Low Risk (2L) from Buy/Low Risk (1L). We expect further litigation over Paxil use in children and while R&D pipeline news will emerge during 2H04, it should not catalyse a rerating of the shares. Forecast 2005 EPS growth is 8% versus 11% for the sector and 8% for the market.

Advair (asthma and COPD) & EPS forecasts cut from above to below consensus

We cut our *Advair* (for asthma and COPD — chronic obstructive pulmonary disease) forecasts by 15% for 2004E and by between 21% and 33% for 2005E-08E. We cut our EPS forecasts by 1% for 2004E, 4% for 2005E and 7% for 2006E.

Paxil (depression) litigation likely to expand

We expect the New York State lawsuit for fraud over alleged suppression of *Paxil* clinical trial data showing increased suicidal tendencies in children and adolescents to result in a fine of US$500m. However, a flood of plaintiff cases may be expected, which will be bad for sentiment, if ultimately hard to prove.

More pipeline news in 2H04

Following modestly encouraging early data on the novel oral anti-cancer drug 572016 at ASCO (American Society of Clinical Oncology), we expect further phase II data on 406381 for arthritis, 353162 for depression and 685698 for allergies. Additionally, an R&D seminar will be held later in the year with further information on certain areas of the pipeline. We do not believe phase II data will drive a major rerating of the shares. Stripping out the underlying business implies a value of £7 billion for the pipeline, or 125p per share, which seems about right given its early stage of development.

2005E P/E discount to sector of 20%, premium of 20% to UK market

On our 2005 forecasts the shares are trading at a 20% discount to the European pharmaceutical sector and a 20% premium to the UK market. However, 2005E EPS growth is 8% versus 11% for the sector and 8% for the market.

We downgrade to Hold/Low Risk (2L) from Buy/Low Risk (1L) with a revised target price of 1,235p from 1,400p, based on a 15% discount to the sector on 2005E EPS forecasts, or a multiple of 15.4x.

Advair (Asthma, COPD) Reassessed

- Asthma treatment remains the key forecast driver and recent data from GOAL study reinforces the benefits of *Advair* in achieving control of the disease
- For COPD mortality data may be needed to drive earlier use and replacement of inhaled steroids alone; physicians, especially in the key US market, remain sceptical of the role and benefits of inhaled corticosteroid (ICS) in COPD
- GSK is unable to promote positive trial data versus *Combivent*, which will reduce its uptake in moderate COPD patients
- Positive results from the TORCH mortality study due in 2006 will be key to broader and deeper use of *Advair* to treat COPD
- Consequently, we reduce our forecasts from above to below consensus

Advair: we scale back our aggressive growth assumptions, and are now below consensus

Figure 1. *Seretide/Advair* Forecast Changes, 2003-07E (Pounds in Millions)

		2003	2004E	2005E	2006E	2007E	2008E
Seretide/Advair	12/02/2004	2,214	2,928	3,876	4,972	5,891	6,182
Seretide/Advair	**24/06/2004**	**2,214**	**2,489**	**3,059**	**3,559**	**3,975**	**4,131**
% change		*0%*	*-15%*	*-21%*	*-28%*	*-33%*	*-33%*
Consensus			2,636	3,146	3,603	3,990	4,429

Sources: GlaxosmithKline (Consensus) and Smith Barney estimates.

Following a review of the recent volume growth in the US and after the American Thoracic Society (ATS) conference in Orlando, we have reduced our forecasts for *Advair* by between 15% and 33%. We have moved from above to below consensus.

We have reduced out forecasts for the following reasons:

- We have lowered our assumed rates of *Advair* market share growth in moderate and severe COPD in the US.
- We have marginally reduced our assumed penetration rates in mild to moderate asthma.
- We have adjusted 2004 forecasts for a weaker US dollar/sterling exchange rate.

Advair in COPD: GSK unable to promote benefits due to narrow wording of approval

GSK presented data at ATS that clearly showed significant improvement in lung function and dyspnoea (breathlessness) compared with *Combivent* (ipratropium and salbutamol combination) in a broad population of COPD patients.

Good data versus Combivent, but FDA will not allow promotional use

Advair is only approved for treatment of COPD associated with chronic bronchitis (and not associated with emphysema). The above trial was conducted in an all-comers population with COPD, including patients with both bronchitis and emphysema. Consequently, the FDA will not allow GSK to publicise the result (no press releases) nor allow it to use the trial result in promotional material.

Physicians we spoke to at ATS suggested that there must have been asthmatics included in this trial, given the dramatic difference between the two drugs.

Bearing in mind that it took two attempts with the FDA to get *Advair* approved (two approvable letters before final agreement on the label), this is perhaps not surprising, as the trial would have been started in the expectation that the label wording would have been broader than it has turned out to be.

It is not clear whether it will be possible to broaden the *Advair* label, or whether the promotional restriction will be lifted. We believe both will be difficult to overcome.

This gagging of apparent superiority of *Advair* will restrict GSK's ability to supplant *Combivent* given together with inhaled corticosteroid, which is GSK's principal competitive target and pricing reference in COPD.

Spiriva launch ongoing

Furthermore, the competitive landscape will toughen with Pfizer/Boehringer Ingelheim's *Spiriva* currently being launched in the US. *Spiriva* benefits from a wider label including use for all COPD patients.

Scepticism about ICS a handicap to use[1]

TORCH may be critical to *Advair*'s fortunes in COPD

- There is a clear lack of consensus among clinicians over the role of inhaled corticosteroids (ICS) in COPD despite the fact that guidelines recommend them in more severe disease.
- We believe that the TORCH (Towards a Revolution in COPD Health) study, GSK's three-year trial investigating the impact of *Advair* on survival, will be critical to reinforcing the marketing message. However, results are not expected before 2006.

Advair is competing against *Spiriva* and physician reluctance to prescribe steroids

Two relatively new treatments have become available in the US for COPD during 2003 and 2004 (both have previously been available in Europe).

- GSK's *Advair* was approved in the US in November 2003 for the treatment of COPD in patients with associated chronic bronchitis.

[1] This section is an extract from our report, *Smith Barney at ATS*, published in May 2004.

- Pfizer/Boehringer Ingelheim's *Spiriva* was approved in the US in February 2004 and although already available, the official 'launch' will take place in the next couple of weeks.

Spiriva has a wider label and is indicated for all COPD patients.

Osteoporosis risk & steroids in COPD

Steroid risk — benefit in doubt . . .

In general, there appears to be a lot of concern within the COPD community over whether the benefits of using ICS outweigh the risks. Although it has not been definitively proved as a side effect of ICS treatment in COPD, one of the main areas of concern appears to be over the potentially increased risk of osteoporosis.

. . . despite guideline changes

Despite this, however, the ATS and European Respiratory Society (ERS) updated their guidelines on the treatment of COPD during the recent ATS conference to confirm that ICS should be used in patients with an FEV1 <50% who have suffered at least one exacerbation (moderate or severe) in the last year.

Advair data remain strong

GSK presented some relatively strong data at ATS reinforcing the role of ICS, and *Advair* in particular, in managing COPD. Highlights included:

COSMIC supports Advair role

- Results from the COSMIC study: a one-year withdrawal of fluticasone after three months' treatment with combined salmeterol/fluticasone (*Advair*) in patients with moderate to severe COPD. This study showed that withdrawal of fluticasone resulted in deterioration of lung function (FEV1 and FEV1/FVC) and an increase in exacerbations.
- Analysis of the results of two trials comparing *Advair* and *Combivent* (ipratropium/albuterol). These demonstrated that *Advair* produced a significant improvement in both lung function and dyspnoea (breathlessness) when compared with *Combivent* over an eight-week period.

Clinicians remain sceptical

In general, we believe clinicians still feel that there is not enough convincing data supporting *Advair* use in moderate disease. In addition, many would apparently prefer to add a standalone steroid (eg *Flovent*) to existing bronchodilators (eg *Spiriva*) rather than switch tack completely by switching to *Advair*.

TORCH may change thinking

TORCH may illuminate Advair's true potential

All the physicians we spoke with felt that GSK's TORCH study had the potential to radically change prescribing practice within COPD.

This is a large, three-year study assessing the effect of *Advair* versus its individual components alone on mortality in COPD. It will also study any negative effects on bone mineral density.

Only long-term oxygen therapy has been shown in prospective studies to have a significant effect on survival in COPD patients so a positive result for *Advair* in this trial would provide a significant boost to the drug. However, we are not expecting results of this trial before 2006. Until the TORCH data are available (assuming a successful study), we anticipate that GSK will have to work hard to win over clinicians and encourage them to prescribe *Advair* for COPD.

Advair in asthma[2]

Advair scores with GOAL — raising control in mild disease

Design of the Advair GOAL trial

At ATS GSK presented further results from the Gaining Optimal Asthma ControL (GOAL) study (some preliminary results had been released at the AAAAI meeting in March 2004). The trial design was as follows:

- N=3,421, double-blind, parallel group. Patients received either *Advair* or fluticasone alone.
- Patients stratified by previous corticosteroid use: S1 = ICS-free, S2 = low-dose ICS, S3 = moderate-dose ICS.
- Phase I — doses stepped up every 12 weeks until total control achieved (or maximum dose reached).
- Phase II — patients remained on this dose for remainder of the year.
- Asthma control was measured using a composite measure of seven goals of GINA (Global Initiative for Asthma)/NIH (National Institute of Health) over an eight-week assessment period.
- The primary endpoint was the proportion of patients achieving well-controlled asthma in Phase I with a number of additional secondary endpoints.

[2] This section is an extract from our report, *Smith Barney at ATS*, published in May 2004.

Results of GOAL — will it promote earlier use of combination treatments?

Overall the study proved very successful. The key highlights included:

Advair: More people to goal . . .

- Significantly more patients achieved total disease control with *Advair* than fluticasone alone across all strata and both phases of the study at a lower steroid dose.
- The risk of exacerbation (annualised rates) was significantly reduced with *Advair.*

. . . and faster

- Patients achieved total control significantly faster with *Advair* than fluticasone — for example, with patients who were previously on ICS, 50% taking *Advair* had achieved total control by 21 weeks whereas it took 45 weeks for 50% of patients taking fluticasone to achieve the same result.

From a physician's point of view, and particularly those who were involved in the study or drafting up guidelines for asthma treatment, this was a very important study.

Mild/moderate asthma still poorly treated

Some physicians feel that asthma is still chronically under-treated, particularly in the mild to moderate disease stages, where patients fluctuate with their disease severity and are often at the risk of exacerbations. Although the GINA guidelines indicate the use of ICS as early as mild persistent disease, the drug is often not prescribed and when it is, it is often only prescribed for a short period of time (up to four weeks). It was felt by the investigators that the results from the GOAL study can be used to:

- Demonstrate to physicians that it is possible to achieve aggressive asthma goals and that they should aim higher in their treatment strategy at all stages of the disease (it was felt that many physicians and patients accept slightly uncontrolled asthma, particularly when it is classified as mild);
- Reinforce the GINA guidelines of ICS use in mild persistent asthma; and
- Encourage doctors to prescribe steroids for longer periods of time to allow the patients to get their asthma fully under control.

Advair best for mild/moderate asthma

Advair is already accepted as an excellent treatment for asthma and is popular in the moderate/severe stages of the disease. Expanding into the milder stages of asthma is one of the key ways for GSK to expand market share and the GOAL study should support this aim.